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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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WEBB ZIESENHEIM LOGSDON ORKIN & HANSON, P.C.
700 KOPPERS BUILDING
436 SEVENTH AVENUE
PITTSBURGH, PA 15219

EXAMINER	
SPIEGLER, ALEXANDER H	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 11/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/242,772	VAN DE VEN ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 25, 2004 has been entered.

Status of the Application

2. Claims 53-58 are pending and are rejected herein. This action is made NON-FINAL. Any objections and rejections not reiterated below are hereby withdrawn. Specifically, all previous rejections have been withdrawn in view of Applicants' cancellation of the previous claims.

Specification

3. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.

(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

In the instant case, the descriptions of the Figures are located at various places throughout the specification. See e.g., pages 25, 50-53, etc. Applicants should amend the specification to include a single section describing the Figures.

Claim Objections

4. The claims are objected to because the Claim 53 should refer to a SEQ ID NO (e.g., SEQ ID NO: 116), rather than (or in addition to) Figure 4A.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 53-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 53-58 are indefinite over "nucleic acid sequence consisting of 7313 bases pairs as depicted in Figure 4A" and "or of the open reading frame of 1500 base pairs starting with the ATG at position 481-483 as depicted in Figure 4A" because it is not clear as to whether this refers only to the length of the claimed sequence or to the specific sequence recited in Figure 4A.

B) Claims 54-57 are indefinite over the recitation of "a nucleic acid sequence derived from a translocation partner of PLAG1" because it is not clear as to what nucleic acid sequences are encompassed by "a nucleic acid sequence derived from a translocation partner of PLAG1." For example, it is not clear if the sequence consists of or comprises a PLAG1 translocation partner; consists of a fragment of a PLAG1 translocation partner; consists or comprises a variant of a PLAG1 translocation partner, wherein the variant may have any number of substitutions, deletions or insertions, etc. Furthermore, the specification does not define this recitation.

C) Claim 58 is indefinite over "an antisense nucleic acid sequence of the nucleic acid sequence according to Claim 53," because it is not clear if this sequence is the same as the complement of Claim 53, a sequence comprising or consisting of the nucleic acid sequence of Claim 53; a sequence sharing an unspecified percent identity or complementarity to the sequence of Claim 53, etc.

New Matter

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 54-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 54 recites, "[a]n isolated hybrid nucleic acid sequence consisting of a fragment of the nucleic acid sequence according to claim 53 fused to *a nucleic acid sequence derived from a translocation partner of PLAG1*..." Applicants' argue support for this recitation can be found on page 3, line 12, page 4, line 37 and page 44, line 4. While these passages provide support for the fusion of PLAG1 and CTNNB1, these passages do support the broader recitation of the fusion between *fragments* of the nucleic acids sequence of claim 53 and "a nucleic acid sequence derived from a translocation partner of PLAG1." The recitation of "a nucleic acid sequence derived from a translocation partner of PLAG1," suggests the claim is drawn to an isolated hybrid consisting of a fusion between fragments of the nucleic acids sequence of claim 53 and *any* "nucleic acid sequence derived from a translocation partner of PLAG1." However, the specification only provides support for the fusion partner consisting of CTNNB1. Accordingly, Claim 54 is considered to encompass new matter.

Claim 57 recites, "[a]n isolated nucleic acid sequence according to claim 55 containing *614 base pairs* corresponding to exon 1 of CTNNB1 fused to exons 2 to 5 of PLAG1." Applicants' argue support for this recitation can be found on page 44, lines 5-9. However, page 44, lines 5-9 states,

> The PCR product *of 605 bp* contains an extra 105 bp, which corresponds to the alternatively spliced exon 2 of PLAG1. It points towards the presence of a related isoform consisting of exon 1 of CTNNB1 and exons 2 to 5 of PLAG1.

Accordingly, there is no support for the recitation of "614 base pairs," and therefore, Claim 57 is constitutes new matter.

Claim 58 recites, "[a]n isolated anti-sense nucleic acid sequence of the nucleic acid sequence according to claim 53 *or fragments thereof* which inhibit the expression of said nucleic acid sequence according to claim 53 *in tumor cells*." Applicants' argue support for this recitation can be found on page 10, lines 17-21. However, page 10, lines 17-21 recites, "[t]he invention for example provides anti-sense molecules or expression inhibitors of the PLAG gene for use in the treatment of diseases involving cells having a non-physiological proliferative capacity by modulating the expression of the gene." Accordingly, because this passage does not support the recitation of "or fragments thereof," or "in tumor cells," Claim 58 constitutes new matter.

Written Description

9. Claims 54, 55 and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 54 is drawn to "[a]n isolated hybrid nucleic acid sequence consisting of a fragment of the nucleic acid sequence according to claim 53 fused to *a nucleic acid sequence derived from a translocation partner of PLAG1*..." Accordingly, claim 54 is drawn to an isolated hybrid nucleic acid consisting of *any* fragment of the nucleic acid sequence according to claim 53 (e.g., a single nucleotide) fused to *any* nucleic acid sequence "derived from a translocation partner of PLAG1." Claim 55 is drawn to *any* fragment of Claim 53 fused to *any* CTNNB1 protein. Claim 58 is drawn to "[a]n isolated anti-sense nucleic acid sequence of the nucleic acid sequence according to claim 53 *or fragments thereof* which inhibit the expression of said nucleic acid sequence according to Claim 53 in tumor cells." Accordingly, claim 58 is drawn to any fragment of the nucleic acid sequence according to claim 53 (e.g., a single nucleotide), which inhibits the expression of said nucleic acid sequence according to Claim 53 in any tumor cell. It is also noted that claims drawn to fragments encompass unspecified nucleic acid substitutions, deletions or insertions, allelic variants, sequences from other species having different functional activities, etc.

The specification discloses that CTNNB1 is a translocation partner of PLAG 1. See e.g., page 3, lines 12-13. Furthermore, the specification teaches a hybrid nucleic acid sequence consisting of exon 1 of CTNNB1 fused to exons 3 to 5 of PLAG1, and exon 1 of CTNNB1 fused to exons 2 to 5 of PLAG1. See e.g., page 44, lines 4-9. However, the specification does not teach isolated hybrid nucleic acid consisting of *any* fragment of the nucleic acid sequence according to claim 53 (e.g., a single nucleotide) fused to *any* nucleic acid sequence "derived

from a translocation partner of PLAG1." Specifically, the specification does not teach any other translocation partners of PLAG1, except that of CTNNB1. Furthermore, the specification does not teach any fragments of the nucleic acid sequence according to claim 53 (e.g., a single nucleotide), which inhibits the expression of said nucleic acid sequence according to Claim 53 in any tumor cell. Furthermore, the specification does not teach nucleic acid substitutions, deletions or insertions, allelic variants, etc. that are encompassed with the claimed invention.

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, only two members (the hybrid consisting of exon 1 of CTNNB1 fused to exons 3 to 5 of PLAG1, and exon 1 of CTNNB1 fused to exons 2 to 5 of PLAG1) have been defined by its structure. Furthermore, the specification does not teach any fragments of the nucleic acid sequence according to claim 53 (e.g., a single nucleotide), which inhibits the expression of said nucleic acid sequence according to Claim 53 in any tumor cell.

It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., other translocation partners of PLAG1, conserved domains of translocation partners of PLAG1, fragments of the nucleic acid sequence according to Claim 53 that inhibit the expression of said nucleic acid sequence in tumor cells, etc.). In the instant case, no such identifying characteristics have been provided for ant of the nucleic acids.

In addition, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he

or she was in *possession* of the invention. The invention is, for purposes of the written description inquiry, *whatever is now claimed* (See page 1117)."

Furthermore, in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus of nucleic acids by only their functional activity, does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention."

Accordingly, because the specification does not disclose or show possession an isolated hybrid nucleic acid consisting of *any* fragment of the nucleic acid sequence according to claim 53 (e.g., a single nucleotide) fused to *any* nucleic acid sequence "derived from a translocation partner of PLAG1" or *any* CTNNB1 protein, nor does the specification teach any translocation partners of PLAG1, other than CTNNB1, the claimed invention lacks an adequate written description. Furthermore, because the specification does not teach any fragments of the nucleic acid sequence according to claim 53 (e.g., a single nucleotide), which inhibits the expression of said nucleic acid sequence according to Claim 53 in any tumor cell, the claimed invention lacks an adequate written description.

Enablement

10. Claims 54-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the cDNA sequence of the PLAG1 (SEQ ID NO: 116), a nucleic acid sequence consisting of the open reading frame of the PLAG1 gene, an isolated hybrid nucleic acid sequence consisting of the exon 1 of CTNNB1 fused to exons 3 to 5 of PLAG1, and exon 1 of CTNNB1 fused to exons 2 to 5 of PLAG1, which can be used in the diagnosis of pleomorphic adenoma cells, does not reasonably provide enablement for an isolated hybrid nucleic acid sequence consisting of any fragment of the nucleic acid sequence according to claim 53 fused to a nucleic acid sequence derived from a translocation partner of PLAG1, wherein the presence of said hybrid nucleic acid sequence allows for the diagnosis of a cell containing said hybrid nucleic acid sequence as any tumor cell, or an isolated hybrid nucleic acid sequence consisting of the exon 1 of CTNNB1 fused to exons 3 to 5 of PLAG1, and exon 1 of CTNNB1 fused to exons 2 to 5 of PLAG1, which can be used in the diagnosis of any tumor cell, or an isolated anti-sense nucleic acid sequence of the nucleic acid sequence according to claim 53 or fragments thereof which inhibit the expression of said nucleic acid sequence according to Claim 53 in any tumor cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure doe not satisfy the enablement requirement s an whether any necessary experimentation is undue (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to: (1) the quantity of

experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 1404.

In the instant case, the specification does not enable one of skill in the art to make and use the claimed invention for the following reasons:

(1) ***Nature of the Invention & Breadth of the Claims***

Claim 54 is drawn to "[a]n isolated hybrid nucleic acid sequence consisting of a *fragment* of the nucleic acid sequence according to claim 53 fused to *a nucleic acid sequence derived from a translocation partner of PLAG1*..." Accordingly, claim 54 is drawn to an isolated hybrid nucleic acid consisting of *any* fragment of the nucleic acid sequence according to claim 53 (e.g., a single nucleotide) fused to *any* nucleic acid sequence "derived from a translocation partner of PLAG1," which can be used in diagnosis any tumor cell. Claim 55 is drawn to *any* fragment of Claim 53 fused to *any* CTNNB1 protein. Claim 58 is drawn to "[a]n isolated anti-sense nucleic acid sequence of the nucleic acid sequence according to claim 53 *or fragments thereof* which inhibit the expression of said nucleic acid sequence according to Claim 53 in tumor cells." Accordingly, claim 58 is drawn to any fragment of the nucleic acid sequence according to claim 53 (e.g., a single nucleotide), which inhibits the expression of said nucleic acid sequence according to Claim 53 in any tumor cell. It is also noted that claims drawn to fragments encompass unspecified nucleic acid substitutions, deletions or insertions, allelic variants, sequences from other species having different functional activities, etc. Furthermore, claims 54-58 are drawn to the diagnosis of *any* tumor cell.

(2) ***Relative Skill of those in the Art, State of the Prior Art, Amount of Direction or Guidance Presented & Presence or Absence of Working Examples***

Applicant discloses two specific hybrids consisting of an isolated hybrid nucleic acid sequence consisting of the exon 1 of CTNNB1 fused to exons 3 to 5 of PLAG1, and exon 1 of CTNNB1 fused to exons 2 to 5 of PLAG1, which can be used to diagnosis of pleomorphic adenoma cells. See e.g., page 44, lines 4-9.

However, the specification does not teach or provide guidance as to the isolated hybrid nucleic acid consisting of *any* fragment of the nucleic acid sequence according to claim 53 (e.g., a single nucleotide) fused to *any* nucleic acid sequence "derived from a translocation partner of PLAG1" or *any* CTNNB1 protein, which can used to diagnose *any* tumor cell. Specifically, the specification does not teach any translocation partners of PLAG1, except CTNNB1. Furthermore, the specification does not teach any fragments of the nucleic acid sequence according to claim 53 (e.g., a single nucleotide), which inhibits the expression of said nucleic acid sequence according to Claim 53 in *any* tumor cell. In addition, the specification does teach any fragments encompassing nucleic acid substitutions, deletions or insertions, allelic variants, sequences from other species having different functional activities, etc. that are encompassed within the claimed invention. With respect to Claims 54-58, the specification does not teach the diagnosis of *any* tumor cell.

The art of Roijer et al. (Genes, Chromosomes & Cancer (1999) 24:78-82, which includes three inventors of the instant invention) teaches that PLAG1 was not activated and/or disrupted in two tumors, and demonstrates the trial and error experimentation required to test three candidate agents N8, HMGIC and HMGIY, for rearrangements and/or abnormal expression. See

abstract. Specifically, Roijer teaches that neither N8 nor HMGIC had 8;12 rearrangements, and are not PLAG1 translocation partners. See e.g., page 82, column 1. Accordingly, Roijer teaches the unpredictable trial and error experimentation used in determining the relationship between PLAG1 and tumor cell detection, and between PLAG 1 and translocation partner detection.

(3) ***Quantity of Experimentation Necessary & the Unpredictability of the Art***

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. In *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art.

In the instant case, the specification does not any translocation partners of PLAG 1, except CTNNB1. More specifically, the specification does not provide any guidance in selecting other translocation partners (or diagnosing tumor cells other than pleomorphic adenoma cells) and therefore, any experimentation to find additional translocation partners of PLAG1 (or other tumor cells that can be detected by PLAG1 fusion hybrids) would require a large amount of trial and error analysis, wherein the results of such analysis would be unpredictable. For example, the skilled artisan would have to experiment with numerous genes that could possibly fuse with PLAG1. Once obtained, any fusion hybrids would then be tested to determine whether these fusion hybrids could be used in diagnostic assays for detecting tumor cells. Specifically, the skilled artisan would necessarily have to carry out extensive assays such as obtaining tumor

samples, preparation of DNA and RNA, isolating YAC clones, DNA sequencing and computer analysis, PCR amplification of genomic DNA, RACE, RT-PCR, positional cloning, gene characterization assays, finding rearrangements in a test gene by FISH, performing RT-PCR with PLAG1 and the test gene using specific primers, obtaining PCR products and determining the activation of PLAG1 expression due to any translocations with the test gene, in order to find any statistically significant expression that can be used in diagnosing tumor cells. Given the lack of direction and guidance as to what genes may be translocation partners of PLAG1, and what types of tumor cells could be diagnosed with said genes, the quantity of this experimentation would be considered undue.

In addition, the experimentation in determining which fragments of the nucleic acid sequences of Claim 53 that can be used in diagnosing tumor cells would be unpredictable. Specifically, the specification does not provide any guidance as to any fragments of the nucleic acid sequences of Claim 53 that can be made into fusion hybrids, which can then be used in diagnosing any tumor cell. This experimentation would require the skilled artisan to determine all of the possible fragments of the sequences of Claim 53, fuse these fragments to translocation partners to form fusion hybrids, and then test these fusion hybrids for their diagnostic potential for a plurality of possible tumors. Furthermore, since claims are drawn to fragments encompassing unspecified nucleic acid substitutions, deletions or insertions, allelic variants, sequences from other species having different functional activities, etc. the skilled artisan would need to experiment to find these fragments that are capable of use for antisense therapy. (See claim 58). Moreover, the specification does not provide any guidance of possible fragments that can be used for antisense therapy.

However, the state of the art has addressed the unpredictability of such antisense therapy. For example, Braasch et al. concludes that major obstacles persist in the art of using antisense oligos in treating disease: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable." See page 4503, paragraphs 1-2. Braasch et al. specifically identify 3 factors that contribute to the unpredictable efficacy of using antisense compounds in general: 1) the variable capability of antisense oligonucleotides to access sites within the mRNA to be targeted; 2) problems pertaining to the delivery and uptake of the antisense oligos by cells, with the result that "the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death"; and 3), that "oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism." See page 4503, paragraphs 1-2.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. elaborates, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA." See page 4503, paragraphs 1-2. The art of Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules." See page 45, third column. Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the

oligo to reach its target, and that "[a]ttempts to describe the *in vivo* structure of RNA, in contrast to DNA, have been fraught with difficulty." See page 3161, second column.

Further, regarding the therapeutic benefit of antisense technology in general, Branch states, "in fact, nucleic acid drugs should not be thought of as magic bullets. Their therapeutic use will require vigilant monitoring. Compared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs extend only across a narrow concentration range. Both *in vitro* and *in vivo*, less than a factor of ten often separates the concentration producing no antisense effect form that producing the full antisense effect. Steep dose-response curves commonly indicate that a drug has multiple, synergistic mechanisms of action. A drug with a narrow therapeutic window can be potent and extremely valuable, but can also be tricky to use safely. Since the ratio of antisense to non-antisense effects drops sharply outside a restricted concentration range, it will be challenging to obtain consistent therapeutic benefit." See page 46, second column.

Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach." See page 495, second column.

Accordingly, in view of the unpredictability in the art and in view of the lack of specific disclosure in the specification, undue experimentation would be required to practice the invention as it is claimed.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 54-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Nollet et al. (Genomics (March 1996) 32: 413-424, previously cited).

Claims 54-55 are drawn to an isolated "hybrid" consisting of a fragment of the nucleic acid sequence according to Claim 53 (e.g., a single nucleotide) fused to a nucleic acid sequence derived from a translocation partner (e.g., CTNNB1), wherein the presence of said hybrid nucleic acid sequence allows the diagnosis of a cell containing said hybrid nucleic acid sequence as a tumor cell. See pages 414-415 and pages 420-421.

Conclusion

13. No claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Alexander H. Spiegler
November 18, 2004

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600